Diploma Course on Research & Development of Products to Meet Public Health Needs

Sponsored by Nagasaki University

in cooperation with Thammasat University, Chulalongkorn University, China Second Military Medical University, Antioquia University and The Graduate School of Pharmaceutical Sciences of The University of Tokyo

in collaboration with WHO and The Pharmaceutical Society of Japan (PSJ)

Nagasaki University, Japan
October 2 - November 8, 2006

Module 1：Course Orientation

2 October, 2006 Monday

0900-0915	Welcome address *President, Prof. Dr. Hiroshi Saitoh, Nagasaki University, Japan*
0915-0945	Objective of the course *Professor Dr. Kenji Hirayama, Director of the course, Nagasaki University, Japan*
0945-1000	Introduction of participants
1000-1030	*Tea break*
1030-1200	Key medical and public health issues, and the need for new products *Dr. Janis Lazdins, WHO/TDR, Geneva*
1200-1300	*Lunch*
1300-1400	Discovery research and product development and the different approaches required for each of them *Dr. Janis Lazdins, WHO/TDR, Geneva*
1400-1500	Stakeholders in Product Research and Development • Large, medium and small pharmaceutical companies • Academic institutions • Clinical Research Organization • Biotech • Regulatory *Prof. Dr. Eiji Uchida, Showa University, Tokyo, Japan*
1500-1530	*Tea break*
1530-1600	Stakeholders in Product Research and Development *Prof. Dr. Eiji Uchida, Showa University, Tokyo, Japan*

Module 2：Drug Development

Drug Discovery

3 October, 2006 Tuesday

0900-1100	History and overview of modern drug discovery *Mr. Nobuhiro Noro, GSK, Japan*
1100-1130	*Tea Break*
1130-1230	From drug target to drug lead *Mr. Nobuhiro Noro, GSK, Japan*
1230-1400	*Lunch*
1400-1530	Drug targets identification and validation in cardiovascular diseases *Dr. Hisashi Ohta, Tsukuba Institute Merck Banyu Pharmaceutical, Japan*

4 October, 2006 Wednesday

0900-1030	Overview of chemistry in drug discovery Hit/lead generation and optimization *Dr. Prof. Tadashi Yoshimoto, Nagasaki University, Nagasaki, Japan*
1030-1100	*Tea break*
1100-1200	Drug discovery for Prion disease *Prof. Shigeru Katamine, Nagasaki University, Nagasaki, Japan*
1200-1330	*Lunch*
1330-1430	Drug targets identification and validation in TB *Assoc. Prof. Dr. Prasit Palithapolkarnpim, BIOTEC, Thailand*
1430-1530	Drug discovery for TB *Dr. Mitsuyoshi Kinoshita, Otsuka pharmaceutical, Osaka, Japan*
1530-1600	*Tea break*
1600-1700	Drug discovery for Trypanosomiasis *Prof. Dr. Kiyoshi Kita, The University of Tokyo, Japan*

5 October, 2006 Thursday

0900-1000	Publications, IPR and patents in drug discovery *Mr. Kenichi Osawa, Merck Banyu Pharma, Japan*
1000-1030	*Tea break*
1030-1130	Publications, IPR and patents in drug discovery (Cont.) *Mr. Kenichi Osawa, Merck Banyu Pharma, Japan*

Chemical Manufacturing and Control (CMC)

6 October, 2006 Friday

0900-1000	Synthesis of active pharmaceutical ingredient *Prof. Dr. Susumi Hatakeyama, Nagasaki University, Japan*
1000-1030	Formulation *Prof. Dr. Susumi Hatakeyama, Nagasaki University, Japan*
1030-1100	*Tea break*
1100-1300	Methods for determination of concentrations in various media by means of spectrometric methods, HPLC, and biological methods *Prof. Dr. Masaaki Kai, Nagasaki University, Japan*
1300-1400	*Lunch*
1400-1530	Stability for drug substance and drug product *Prof. Dr. Hiroaki Nagaoka, Nagasaki International University, Japan*
1530-1600	*Tea break*
1600-1700	Example: Antimalarial drug, dihydroartemisinin *Assoc. Prof. Supornchai Matangkasobat, Mahidol University, Thailand*

7 October, 2006 Saturday

0900-1030	Development of specification *Prof. Dr. Hiroaki Nagaoka, Nagasaki International University, Japan*
1030-1100	*Tea break*
1100-1200	Quality assurance/quality control *Prof. Dr. Hiroaki Nagaoka, Nagasaki International University, Japan*
1200-1300	*Lunch*
1300-1530	Regulatory (with an example of a drug CMC requirement) *Prof. Dr. Hiroaki Nagaoka, Nagasaki International University, Japan*
1530-1600	*Tea break*
1600-1630	Naming the New Chemical Entity (NCE) *Prof. Dr. Hiroaki Nagaoka, Nagasaki International University, Japan*

Pre-clinical Development

Pharmacological development

9 October, 2006 Monday

0900-1100	Pharmacological data in new drug application *Dr. Shunsuke Ono, University of Tokyo, Japan*
1100-1130	*Tea break*
1130-1230	Methods in pharmacological R&D (1) *Dr. Hiroyuki Itoh, Astellas Pharma Inc, Japan*
1230-1330	*Lunch*
1330-1430	Methods in pharmacological R&D (2) *Dr. Hiroyuki Itoh, Astellas Pharma Inc, Japan*
1430-1500	Discussion *Drs. Shunsuke Ono and Hiroyuki Itou*
1500-1530	*Tea break*
1530-1630	The cure oriented therapeutics for chronic renal failure with gene therapy *Dr. Tsutomu Kurosawa, Osaka University, Japan*

Toxicology

10 October, 2006 Tuesday

0900-1000	Principles of toxicology *Assoc. Prof. Dr. Wongwiwat Tassaneeyakul, Kon Kaen University, Thailand*
1000-1100	Toxicological tests: *in vitro & in vivo:* acute, subacute, chronic, special organ toxicology, reproduction toxicology, teratogenicity, mutagenicity, carcinogenicity studies *Assoc. Prof. Dr. Wongwiwat Tassaneeyakul, Kon Kaen University, Thailand*
1100-1130	*Tea break*
1130-1300	Scheduling of toxicological studies in the development plan, the registration requirements, human & animal pharmacology, the proposed clinical application and the forms of administration. *Dr. Soisanwan Satarug, University of Queensland, Australia*
1300-1400	*Lunch*
1400-1530	Continuous monitoring of the correlation between new toxicological findings and the unwanted events observed in humans up till now. *Dr. Soisanwan Satarug, University of Queensland, Australia*

Pre-clinical Pharmacokinetics

11 October, 2006 Wednesday

0900-1030 Principles of pharmacokinetics: ADME processes
Assoc. Prof. Dr. Wongwiwat Tassaneeyakul, Kon Kaen University, Thailand

1030-1100 *Tea break*

1100-1230 Pharmacokinetic data analysis & pharmacokinetic parameters
Assoc. Prof. Dr. Wongwiwat Tassaneeyakul, Kon Kaen University, Thailand

1230-1330 *Lunch break*

1330-1530 Transferability of the pharmacokinetic findings in animals to humans
Investigating toxicological problems - practices and pitfalls
Dr. Soisanwan Satarug, University of Queensland, Australia

12 October, 2006 Thursday

1000-1200 Visit animal facility for medical research
Dr. Kazuki Osawa, Nagasaki University, Japan

1500-1630 Evaluation of viability (risk and benefit) for further development (case study)
Dr. Tadaaki Taniguchi, Japanese Association of Pharmaceutical Medicine (JAPHMED), Merck Banyu Pharma, Japan

Clinical Development

Clinical Trial

13 October, 2006 Friday

0900-1100 Overview of clinical development

- Assessment of pre-clinical information
- Clinical development plan
- Application of pharmacokinetics and pharmacodynamics in drug development
- Dose selection and regimen

Dr. Tadaaki Taniguchi, Japanese Association of Pharmaceutical Medicine(JAPHMED), Merck Banyu Pharma, Japan

1100-1130 *Tea break*

1130-1200 The various investigational phases of clinical research (Phases I-IV)
Dr. Tadaaki Taniguchi, Japanese Association of Pharmaceutical Medicine (JAPHMED), Merck Banyu Pharma, Japan

1200-1300 *Lunch*

1300-1500 Human pharmacokinetics:

- Definition and significance of pharmacokinetic parameters (absorption, bioavailability, binding to proteins, distribution, clearance, elimination half life, AUC)
- Special human-pharmacokinetic studies e.g. bioavailability studies of multiple-dose, interaction studies, pregnancy, liver disease *etc*.

Assoc. Prof. Dr. Wongwiwat Tassaneeyakul, Kon Kaen University, Thailand

14 October, 2006 Saturday

0900-1000 Therapeutic exploratory (with example)
Dr. Kenji Nonaka, Japanese Association of Pharmaceutical Medicine (JAPHMED), Merck Banyu Pharma, Japan

1000-1100 Therapeutic confirmatory (with example)
Dr. Kenji Nonaka, Japanese Association of Pharmaceutical Medicine(JAPHMED), Merck Banyu Pharma, Japan

1100-1130 *Tea Break*

1130-1230 Therapeutic use (with example)
Dr.Kimihiro Kasamo, Japanese Association of Pharmaceutical Medicine(JAPHMED), Merck Banyu Pharma, Japan

1230-1330 *Lunch*

1330-1500 Safety monitoring and reporting in clinical trials

- Basic principles and evaluation of investigational results (Phase-I and early Phase-II), with a view to further Development
- Basic principles for decisions regarding further development or discontinuation of a development project

Dr. Kimihiro Kasamo, Japanese Association of Pharmaceutical Medicine(JAPHMED), Merck Banyu Pharma, JapanTea break

1500-1530 *Tea Break*

1530-1630 Pharmacogenomics
Dr. Shyh-Yuh Liou, Japan Section GlaxoSmithKline, Japan

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Study design

16 October, 2006 Monday

0900-1030 Study design
- Possible study designs taking into account ethical aspects, indication, controls, patient population, location of the trial centers
- Trial design (parallel group design, cross over design, factorial design, group sequential design)
- Design techniques to avoid bias (blinding, randomization)

Prof. Dr. L. Jeyaseelan, Christian Medical University, Vellor, India

1030-1100 *Tea break*

1100-1230 Study design (Cont.)
- Multi centers trials
- Type of comparison
- Outcome measurements

Prof. Dr. L. Jeyaseelan, Christian Medical University, Vellor, India

1230-1330 *Lunch*

1330-1500 Statistical considerations
- Biostatistics in the planning phase (estimate of number of cases, randomization, statistical models, definition of end-points, planning of the subsequent evaluation)
- Statistical analysis plan
- Analysis sets: full analysis set, per protocol set, missing values and outliers

Prof. Dr. L. Jeyaseelan, Christian Medical University, Vellor, India

1500-1530 *Tea break*

1530-1700 Statistical considerations (Cont.)
- Data transformation
- Method of statistical analysis (estimation, confidence intervals, hypothesis testing, evaluation of safety and tolerability)
- Statistical analysis report

Prof. Dr. L. Jeyaseelan, Christian Medical University, Vellor, India

Regulatory Issues

17 October, 2006 Tuesday

0900-1030 Regulatory aspects of clinical development
Prof.Dr. Koji Kawakami, Kyoto University, Kyoto, Japan

1030-1100 *Tea break*

1100-1230 Special topics:
- Genetic engineer product
- Gene therapy and stem cells

Prof. Dr. Koji Kawakami, Kyoto University, Kyoto, Japan

1230-1330 *Lunch*

1330-1500 Example of Clinical Drug development in India - Miltefosine trial
Prof. Dr. Juntra Karbwang, WHO/TDR, Switzerland

Traditional Medicine

18 October, 2006 Wednesday

0900-1030 Introduction of Traditional Medicine: Alternative but rational approach
Professor Dr. Kiichiro Tsutani, University of Tokyo, Japan

1030-1100 *Tea break*

1100-1200 Guidance on herbal medicine
Professor Dr. Kiichiro Tsutani, University of Tokyo, Japan

1200-1300 *Lunch*

1300-1500 Regulation for traditional medicine development
Japan: *Dr. Ichiro Arai, Manager, R&D Strategy Dept. Tsumura & Co.*
China: *Professor Dr. Luping Qin, China*

1500-1530 *Tea break*

1530-1700 Example: Herbal medicine to modern medicine
Example: traditional medicine development
Professor Dr. Luping Qin, Second Military Medical University, China

Module 3: Vaccine Development

Vaccine Discovery

19 October, 2006 Thursday

0900-0930	Historical of vaccine Discovery *Dr. Howard Engers, AHARI, Ethiopia*
0930-1030	Overview of modern vaccine discovery *Dr. Howard Engers, AHARI, Ethiopia*
1030-1100	*Tea break*
1100-1200	Screening for antigens *Prof. Dr. Kenji Hirayama, Nagasaki University, Japan*
1200-1330	*Lunch*
1330-1430	Evaluating antigens *Prof. Dr. Kenji Hirayama, Nagasaki University, Japan*
1430-1500	*Tea break*
1500-1600	Visiting Vaccine Discovery Laboratory Institute of Tropical Medicine, Nagasaki University

20 October, 2006 Friday

0900-1030	Adjuvant - *Dr. Howard Engers, AHARI, Ethiopia*
1030-1100	*Tea break*
1100-1200	Alternatives to antigens: DNA vaccine, Live or attenuated pathogen *Dr. Howard Engers, AHARI, Ethiopia*
1200-1330	*Lunch*
1330-1430	Selection of development candidate and back-ups *Dr. Howard Engers, AHARI, Ethiopia*
1430-1500	*Tea break*
1500-1630	Efficacy, toxicity, route if immunization, price, stability, cold chain, *Dr. Howard Engers, AHARI, Ethiopia*

21 October, 2006 Saturday

0900-1030	Malaria vaccine discovery *Prof. Dr.Weiqing Pan, Second Military Medical University, China*
1030-1100	*Tea break*
1100-1200	Cholera vaccine discovery *Dr. Masahiko Ehara, Nagasaki University, Japan*
1200-1300	*Lunch*

1300-1400 West Nile Fever vaccine discovery
Prof. Dr. Kouichi Morita, Nagasaki University, Japan

1400-1500 Oral vaccine discovery
Dr. Takeshi Arakawa, Ryukyu University, Japan

Antigen Development

23 October, 2006 Monday

0900-1030 <**Antigen Development**>:
1. History of Vaccine Development
2. Down period-Try and error period
3. The 2nd period - Toxoid vaccine
4. The 3rd period - Virus vaccines period
5. The 4th period - Genetic engineering period
Dr. Kiyoshi Horiuchi, GlaxoSmithKline KK, Tokyo, Japan

1030-1100 *Tea break*

1100-1230 Continued
Dr. Kiyoshi Horiuchi, GlaxoSmithKline KK, Tokyo, Japan

1230-1330 *Lunch*

1330-1430 1. Process of Vaccine Production
2. Materials for vaccines
2-1 Vaccine strain
2-2 Media, cells and animals used for vaccine product
3. Cell culture
4. Purification
5. Inactivation
6. Adjustment of the final bulk
7. Aliquoting, lyophilising and shipping
Dr. Kiyoshi Horiuchi, GlaxoSmithKline KK, Tokyo, Japan

1430-1530 *Tea break*

1530-1600 Continued
Dr. Kiyoshi Horiuchi, GlaxoSmithKline KK, Tokyo, Japan

Clinical Development

24 October, 2006 Tuesday

0900-1030 <**Quality Assurance of Vaccine**>
1. Necessity of Quality Control
2. Definition of Biological Products
3. Standard Preparations
4. In-process Control and Tests
5. national Control Authority
6. Efficacy Control of Vaccines
7. Safety Control

Dr. Kiyoshi Horiuchi, GlaxoSmithKline KK, Tokyo, Japan

1030-1100 *Tea break*

1100-1230 Continued
Dr. Kiyoshi Horiuchi, GlaxoSmithKline KK, Tokyo, Japan

Pre-Clinical Development

25 October, 2006 Wednesday

0900-1030 Animal model used in pre-clinical studies
Dr. Shigeyuki Kano, International Medical Center of Japan, Tokyo

1030-1100 *Tea break*

Clinical Development

Overview

1100-1130 Assessment of pre-clinical information
Dr. Pele Chong, Taiwan

1130-1230 Clinical development plan
Professor Dr.Kenji Hirayama, NagasakiUniversity, Japan

1230-1330 *Lunch*

1330-1430 Application of immunogenicity for vaccine development
Dr. Shigeharu Ueda, The Research Foundation for Microbial Diseases of Osaka University (BIKEN), Japan

1430-1500 *Tea break*

1500-1600 Dose selection and regimen
Dr. Shigeharu Ueda, The Research Foundation for Microbial Diseases of Osaka University (BIKEN), Japan

Pre-Clinical Development

26 October, 2006 Thursday

0900-1030	Safety assessment Toxicity test for animal: regional complications, systemic toxicity such as fever, anaphylactic shock *Mr. Nobuhiro Noro, GlaxoSmithKline KK, Tokyo, Japan*
1030-1100	*Tea break*
1100-1230	Immunogenicity assessment *Mr. Nobuhiro Noro, GlaxoSmithKline KK, Tokyo, Japan*
1230-1330	*Lunch*
1330-1430	Regulatory *Mr. Yasushi Yoshino, Dr. Masaru Iwasaki, GlaxoSmithKline KK, Tokyo, Japan*

Module 4: Diagnostic Development

27 October, 2006 Friday

0900- Discovery and development of diagnostic tools:
Necessity assessment, Principles and technology selection
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

Prototype production and assessment
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

Scale-up, manufacture and control
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

Scale-up, manufacture and control (Cont.)

Development of kits
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

Quality assurance/quality control: evaluation of efficacy after application
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

Clinical development: validate prototype, manufacture pilot lot, initiate clinical trial
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

-1730 Clinical development: Supply chain logistics and production, Statistical consideration, regulatory issues
Dr. Masato Sasaki, Roche Diagnostics KK, Tokyo, Japan

Module 5: Good Clinical Practice

Ethics in research and Ethics Committee

30 October, 2006 Monday

0900-1000	Ethics Codes and Guidelines *Dr.Vichai Chokevivat, FERCAP, Thailand*
1000-1100	Principles of Research Ethics *Prof.Dr. Cristina Torres, FERCAP, Thailand*
1100-1130	*Tea break*
1130-1230	Case study
1230-1400	*Lunch*
1400-1500	Research methodology and ethical issues (1) Traditional medicine *Dr. Vichai Chokevivat, Director, Department of Alternative Medicine, MOH, Thailand*
1500-1600	Research methodology and ethical issues (2) Genetic study *Prof. Dr. Kenji Hirayama, Nagasaki University, Japan*
1600-1630	*Tea break*
1630-1730	Case study

31 October, 2006 Tuesday

0900-1030	Human Subject Protection and Ethics Committees *Prof. Dr. Cristina Torres, FERCAP, Thailand*
1030-1100	*Tea break*
1100-1230	Human Subject Protection and Ethics Committees Cont. *Prof.Dr. Cristina Torres, FERCAP, Thailand*
1230-1400	*Lunch*
1400-1500	Data and Safety Monitoring Board (DSMB) *Dr. Allan Johansen, Roche Products Pty limited, Australia*
1500-1630	Case study
1630-1730	Monitoring and Auditing Ethics Committee *Prof. Dr. Cristina Torres, FERCAP, Thailand*

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1 November, 2006 Wednesday

Quality Standards

0900-0930 Concept of Good Clinical Practice
Dr. Allan Johansen, Roche Products Pty limited, Australia

0930-1130 Responsibilities
Sponsor (*Dr. Allan Johansen)*
Investigators (*Prof. Kenji Hirayama*)
IRB (*Prof. Cristina Torres*)
Monitors (*Prof. Juntra Karbwang*)
DSMB (*Dr. Allan Johansen*)

1130-1230 Audit and Inspection
Dr. Allan Johansen, Roche Products Pty limited, Australia

1230-1400 *Lunch*

1400-1530 New Asymmetric Catalysis; Leading to the synthesis of Tamiflu
Prof.Dr. Masakatsu Shibasaki, The University of Tokyo, Japan

2 November, 2006 Thursday

In the morning: Field Trip to Kaketsuken, Kumamoto by Bus:

1300-1700 Good Manufacturing Practice (GMP)
Good Laboratory Practice (GLP)
Dr. Tetsuro Satoh, Kaketsuken, Kumamoto, Japan

Visit GMP lab and GLP lab and Plant for vaccine production

3 November, 2006 Friday Holiday

Module 6: Clinical Data Management

6 November, 2006 Monday

0900-1000	Overview of clinical data management Data management plan *Dr. Charcrin Na-Bangchang, TU-CDMC, Thailand*
1000-1030	Statistical Analysis Plan (SAP) Data: primary & secondary data *Dr. Rui Wang, SMMC-CDMC, China*
1030-1100	*Tea break*
1100-1230	Data capture , development of database *Dr. Arunachalam Rajagopal, CMC-CDMC, India*
1230-1330	*Lunch*
1330-1400	Data entry, data verification, data validation, audit trail Data clarification process Data query and resolution *Dr. Jose Fernando Florez Arango, CMC-CDMC, Colombia*
1400-1500	Data transform process ▪ Adverse Event Dictionary ▪ Drug Dictionary *Dr. Sangkae Chamnanvanakij, TU-CDMC, Thailand*
1500-1530	*Tea break*
1530-1700	Statistical analysis *Dr. Rui Wang, SMMC-CDMC, China*
1700-1800	Quality Control & Assurance (QC & QA) Standard Operating Procedures (SOPs) *Dr. Jose Fernando Florez Arango, CMC-CDMC, Colombia*

Module 7: Post-registration Activities

7 November, 2006 Tuesday

0900-1100	Stakeholders to be involved in making product development work for the intended beneficiaries *Prof. Dr. Chitr Sitthi-amorn, Chulalongkorn University, Thailand* *Prof. Dr. Kazuko Kimura, Kanazawa University, Japan* *Dr. Kihito Takahashi, Japanese Association of Pharmaceutical Medicine (JAPHMED), Merck Banyu Pharma, Japan*
1100-1130	*Tea break*
1130-1230	Stakeholders to be involved in making product development work for the intended beneficiaries
1230-1330	*Lunch*
1330-1430	Public private partnership *Prof. Dr. Kazuko Kimura, Kanazawa University, Japan* *Prof. Dr. Chitr Sitthi-amorn, Chulalongkorn University, Thailand*
1430-1500	*Tea break*
1500-1700	Pharmacoeconomics *Prof. Dr. Kiichiro Tsutani, University of Tokyo, Japan*

8 November, 2006 Wednesday

0900-0930	Closing Ceremony *Mr. Yukihide Hayashi, Ministry of Education, Culture, Sports and Technology (MEXT), Japan* *Prof.Dr. Hiroshi Saito, President, Nagasaki University* *Prof. Dr. Yoshiki Aoki, Dean, Institute of Tropical Medicine, Nagasaki University* *Prof. Dr. Masao Tomonaga, Dean, Graduate School of Biomedical Sciences, Nagasaki University, Japan* *Prof. Dr. Shigeru Kohno, Dean, Faculty of Medicine, Nagasaki University*
0930-1030	Improving the quality of new products in health systems: International network of rational use of drugs *Prof. Dr. Chitr Sitthi-amorn, Chulalongkorn University*
1030-1100	*Tea break*
1100-1230	Post-marketing product vigilance *Dr. Janis Lazdins, WHO/TDR, Geneva, Switzerland* *Prof. Dr. Yupin, FDA, Thailand*
1230-1330	*Lunch*
1330-1500	Intellectual Property Rights Protection in Developing Countries *Prof. Dr. Hiroko Yamane, Graduate Institute for Policy Studies, Japan*